

**REMARKS**

Claims 1-9 and 17-23 are pending. Claims 1-7 and 9 are newly cancelled. Claim 8 is newly amended. Support for the amendment is found throughout the specification and claims as originally filed and is discussed further below. No new matters and no new issues after-final have been entered.

***35 U.S.C. § 102(b)***

The rejection of Claims 8, 17-18, 20 and 22-23 is maintained under 35 U.S.C. 102(b) as being anticipated by Weinstock et al. (WO 99/33479).

Anticipation requires that the purported prior art reference disclose each and every limitation of the claim. *Atlas Powder Company et al. v. IRECO incorporated et al.*, 190 F.3d 1342, 1347 (Fed. Cir. 1999).

Applicant respectfully traverses on the grounds that all the limitations of the instantly claimed method are not taught by the cited reference of Weinstock et al. (WO 99/33479). Specifically, after administering a helminthic parasite preparation, WO 99/33479 teaches methods of assessing the presence of a Th1 or a Th2 response, while the instant claims recite steps for determining the level of regulatory T cell activity. WO 99/33479 does not mention T regulatory cells, nor the cytokines they secrete, nor their distinguishing cell markers, nor their activity, all of which are encompassed by the instant claims.

WO 99/33479 discloses methods of treating diseases associated with an aberrant/enhanced Th1 response by administering a helminthic parasite preparation. WO 99/33479 discloses the determination of Th1 and Th2 responses by measuring the production of various cytokines and cell surface markers after administering a helminthic parasite preparation in order to show efficacy of the treatment. Specifically, in section D, entitled "Determination of Th1 and Th2 responses", WO 99/33479 discloses:

" In order to show the efficacy of the present invention, the Th1 and Th2 response must be distinguished. Metawali et al., 1996, J. of Immunol. 157:4546 has shown that in mice, it is possible to distinguish a Th1 from a Th2 response by histologic analysis, and by analysis of cytokine and immunoglobulin profiles. Further, Sandor et al., 1990, J. of Exp. Med-171:2171 has shown that cell surface expression of Fcγ3 and MHC Class II molecules afford discrimination. In this procedure, small bowel and colon are examined histologically to determine the degree of mucosal inflammation, eosinophilia and mastocytosis. The latter cell types are indicative of a Th2 response. Mesenteric lymph nodes (MLN) and spleens can be dissociated into single cell suspensions for in vitro culture in microwell plates. Cells (1-2 x 10<sup>7</sup>/well) in complete RPMI medium are cultured for up to 72 h in the presence or absence of worm antigen or anti-CD3 and then the supernatants are assayed for cytokines and immunoglobulins. IFN-γ, TNFα and IgG2a characterize a Th1 response, whereas IL-4, IL-5, IgE and IgG1 typify a Th2 reaction. Also, serum can be assayed for cytokine and immunoglobulin concentrations. Furthermore, dispersed inflammatory leukocytes are examined by flow cytometry for Fcγ3 expression on macrophages (Th1) and MHC Class II expression on B cells (Th2). Controls include serum, MLN and spleens from appropriate age-matched, littermate mice that hosted no parasite. Also, there are other markers of the Th1 vs Th2 responses", emphasis added, pages 21-22 of the instant specification.

In contrast to WO 99/33479, which looks at Th1 and/or Th2 cell activity, the instantly claimed invention is directed to a method directed at determining regulatory T cell activity. This distinction is illustrated in the first sentence of the instant "Summary of the Invention" which states:

" The present invention is based on the finding that parasite preparation can alter the activity of regulatory T cells in the treatment of Th1 or Th2 related disease", emphasis added, page 4 of the instant specification.

Thus, the focus of the instantly claimed methods is on markers and cytokines of T regulatory T cells, as opposed to markers and cytokines of Th1 T cells and/or Th2 T cells as taught by WO 99/33479.

As disclosed in the specification, T regulatory cells regulate Th1 and Th2 cells.

" These regulatory T cells (Tr cells) express a transmembrane protein (called CD25) that is alpha chain of the receptor for interleukin-2 (IL-2). Like other T cells, they also express the  $\alpha\beta$  (alpha-beta) T-cell receptor for antigen (TCR) and can only be activated if it binds to the peptide-class II MHC molecule, or in the case of CD8 regulatory cells Class I MHC, for which it is specific. However, if activated, they begin to secrete large amounts of interleukin 10 (IL-10) and often some transforming growth factor-beta (TGF- $\beta$ ) as well. Both these lymphokines are powerful immunosuppressants inhibiting Th1 help for cell-mediated immunity and inflammation, Th2 help for antibody production, and, possibly, the action of CD8<sup>+</sup> cytolytic T lymphocytes (CTL)", emphasis added, page 4 of the instant specification.

The instant specification teaches that only regulatory T cells are known to express *Foxp3*, page 66, line 21, and further discloses that markers of these regulatory T cells include secretion of increased amounts of IL-10 and/or TGF $\beta$ , decreased amounts of IFN $\gamma$ , and expression of a high level of *Foxp3* transcript, and its protein product Scurfin:

"... the term "regulatory T cells" refers to a lymphocyte cell population which secretes at least 2-fold increase (e.g., 3-fold, 4-fold, 5-fold, 6-fold, 8-fold, 10-fold or more) of IL-10 and/or TGF $\beta$ , as compared to nave T cells. The determination of IL-10 or TGF $\beta$  secretion is known in the art. For example, it may be determined by culturing the cells *in vitro* for 24 or 48 with or without a T cell stimulant like anti-CD3 and then assaying the culture supernatant for these cytokines using cytokine specific ELISAs. In addition, regulatory T cells of the present invention is also characterized by a high level of FoxP3 transcript as compared to other types of T cells (e.g., naive T cells). ... Alternatively, FoxP3 protein product, Scurfin, can be detected by Western blotting analysis as known in the art, e.g., using Goat Anti-FoxP 3 (FoxP3) Polyclonal Antibody (Catalog Number ab248 1, Novus Biologicals, Littleton, Colo.). Optionally, the regulatory T cells may also make much less IFN $\gamma$  as compared to other T cells (e.g., nave T cells), i.e., at least 2-fold, preferably 3-fold, 4-fold, 5-fold, 6-fold, 7-fold, 8-fold, 10-fold or less. Also optionally, regulatory T cells also can be detected by using intracytoplasmic flow analysis to detect T cells expressing IL10 and/or TGF $\beta$  but little or no IFN $\gamma$ . Additional optional markers as described herein below may also be used for

detecting regulatory T cells or the activity of regulatory T cells", emphasis added, pages 10-11 of the instant specification.

Thus, the instant claims for treating a Th1 or Th2 related disease with a helminthic preparation comprise determining the level of regulatory T cell activity, a limitation not taught by WO 99/33479. WO 99/33479 teaches methods of assessing Th1 and/or Th2 cell activity, but does not teach a method comprising the step of determining the activity of regulatory T cell activity, as required by the instant claims. Specifically, WO 99/33479 does not teach a method encompassing the steps of looking at differential expression of individual markers and/or cytokines, e.g., FoxP3, CD25, or a combination of markers and/or cytokines, in order to determine the activity of regulatory T cells, as required by the instant claims.

Because WO 99/33479 does not teach a method comprising determining the level of regulatory T cell activity as required by the instant claims, Applicant respectfully submits that WO 99/33479 is not prior art, and accordingly does not anticipate the instant claims.

***35 U.S.C. § 112, New Matter***

Claims 8 and 17-23 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one of skill in the relevant art that the inventor(s), at the time the invention was filed, had possession of the claimed invention.

The Office Action contends that the phrase "and determining the level of regulatory T cell activity, wherein an increase in regulatory T cell activity after said administering is indicative of successful treatment", which is recited in independent claim 8, is new matter. Applicant has amended claim 8 by deleting the last part of the phrase, specifically deleting "wherein an increase in regulatory T cell activity after said administering is indicative of successful treatment".

Applicant respectfully traverses on the grounds that support for Claim 8, as newly amended, is indeed found in the specification.

Specifically, the specification teaches determining the level of regulatory T cell activity:

"The activity of regulatory T cell may be measured by monitoring the level of a regulatory T cell internal marker (e.g., a transcription factor such as FoxP3 mRNA or its protein product Scurfin, Smad7, Gata3, or Tbet (*Tbx21*)), or a regulatory T cell surface marker (e.g., CD4, CD45RB<sup>lo</sup>, CD45Rc, Cytolytic T lymphocyte associated antigen 4 (CTLA-4), Ox40, 4-1BB, CD25, CD103, CD62L,  $\alpha_E\beta$  integrin, latency-associated peptide (LAP) or glucocorticoid induced TNF receptor family related protein (GITR), Experimental allergic encephalitis (EAE), chemokine receptor CCR5, TI-ST2) or a secreted marker (e.g., IL4, IL13, IL-5, IL-10, TGF $\beta$ ). An increased regulatory T cell activity may be represented by an increase (e.g., FoxP3, Ox40, 4-1BB, CD4, CTLA-4, CD25, CD103, CD62L,  $\alpha_E\beta$  integrin` LAP, GITR, EAE, CCR5, TI-ST2, IL-10, TGF $\beta$ ) or a decrease (e.g., D45Rc), in the level of a regulatory T marker, by at least 40%, e.g., 50%, 80%, 100%, 2 fold, 4 fold, 6 fold, 8 fold, 10 fold, or more, measured according to methods known in the art and as described herein", page 11, line 20, to page 12, line 2, of the instant specification.

Independent Claim 8, as newly amended, is drawn to a method for treating an animal with a Th1 or Th2 related disease by administering a helminthic parasite preparation that alters a regulatory T cell activity to said animal; and determining the level of regulatory T cell activity. Support for the method of Claim 8 is exemplified in the working examples disclose in pages 66-67, and Figures 20 and 21 in a mouse model of colitis. Colitis is thought to have both autoimmune and etiological components, and thus the claim is not limited to autoimmune disease.

The treatment method of claim 8 can be applied when optimizing dosage. The specification discloses on page 34, that the amount or dosage of a helminthic parasite preparation may vary depending on the disease being treated or prevented and the helminthic parasite, whether it is being administered intact, or as an egg, larvae, extract or cercariae, and that the dosage may be monitored by measuring Th1, Th2 or regulatory cell responses.

The specification discloses that the regulatory T cell activity can be measured by an internal marker, a cell surface marker or a secreted marker as described herein, page

36, lines 13-14, thus providing support for claims 17, 20 and 22. The specification discloses that useful internal markers for regulatory T cells include, but are not limited to, transcription factors such as Scurfin, Smad7, Gata3, and Tbet, thus providing support for claims 18 and 19. The specification discloses that useful surface molecules for regulatory T cells include, but are not limited to, CD4, CD45RB<sup>lo</sup>, CD45Rc, Cytotoxic T lymphocyte associated antigen 4 (CTLA-4), Ox40, 4-1BB, CD25, CD103, CD62L, α<sub>E</sub>β integrin, latency-associated peptide (LAP) or glucocorticoid induced TNF receptor family related protein (GITR), chemokine receptor CCR5, TI-ST2, providing support for claim 21. The specification discloses that useful secreted molecules for regulatory T cells include, but are not limited to IL-5, IL-10 and TGFβ provide support for claim 23.

The Office Action in noting that the instant claims, encompass any Th1 or Th2 disease, states that the portion of the specification (page 5 and original claim 9), previously cited by Applicant "deals only with autoimmune diseases and allergic diseases". Applicant respectfully contends that the diseases encompassed by the instant claims as newly amended are not limited to autoimmune diseases and allergic diseases, noting that the specification discloses on page 16, lines 11-12, in the section entitled "Diseases Treatable According to the Invention" that "examples of treatable diseases, according to the invention, include, but are not limited to, Th1 related and Th2 related diseases".

Thus, Applicant respectfully submits that the claims as newly amended are fully supported by the specification and the claims as originally filed.

**35 U.S.C. § 103(a)**

Claims 8 and 17-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weinstock et al (WO 99/33479).

Applicant respectively traverses.

*Graham v. John Deere Co.*, 338 U.S. 1, 148 USPQ 459 (1966), recently reaffirmed by *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 82 USPQ2d 1385

(2007), provides the analytical framework for determining obviousness. Under *Graham*, obviousness is a question of law based on underlying factual inquiries that address (1) the scope and content of the prior art, (2) the differences between the claimed invention and the prior art, and (3) the level of ordinary skill in the pertinent art. Evidence of secondary factors (e.g., commercial success, long-felt but unmet need, and unexpected results) are also given weight in the analysis. Moreover, to establish a *prima facie* obviousness rejection of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974).

Predictability is required in maintaining a legal conclusion of obviousness under both KSR and the USPTO published guidelines.

Independent Claim 8, as newly amended, is drawn to a method for treating an animal with a Th1 or Th2 related disease by administering a helminthic parasite preparation that alters a regulatory T cell activity to said animal; and determining the level of regulatory T cell activity.

The Office Action indicates that it would have been obvious for the skilled artisan to use the regulatory T cell markers recited in claims 19 and 21 in the methods of WO 99/33479 "for determination of Th1 and Th2 responses after treatment with the claimed composition 'in order to show efficacy of their method' " "since the use of screening of the recited T cell activation markers is well known in the art".

As described above, WO 99/33479 discloses methods of treating diseases associated with an aberrant/enhanced Th1 response by administering a helminthic parasite preparation. WO 99/33479 discloses the determination of Th1 and Th2 responses by measuring the production of various cytokines and cell surface markers after administering a helminthic parasite preparation in order to show efficacy of the treatment.

However, as also described above, WO 99/33479 does not teach a method comprising determining regulatory T cell activity as required by the instant claims.

Further, the instant specification discloses that at the time of the invention, the role of regulatory cells in a treatment comprising the administration of a helminthic preparation for a disease with an aberrant Th1 response was not known.

" It remains unknown whether regulatory T cells play a role in the prevention or treatment of Th1 or Th2 related diseases using a helminthic parasite preparation", page 4, lines 20-21.

As discussed above, predictability is required in maintaining a legal conclusion of obviousness under both KSR and the USPTO published guidelines. However, the office action provides no grounds on which one of skill could predictably ascertain that regulatory T cells play a role in the treatment of Th1 or Th2 related diseases comprising administering a helminthic parasite preparation.

The Office Action indicates that the use of screening of the recited T cell activation markers is well known in the art. However, the instant claims are not drawn to a method of treatment comprising determining the level of T cell activation markers. Instead, the instant claims are drawn to a method of treatment comprising determining the level of regulatory T cell activity by determining in some embodiments the level of regulatory T cell markers.

Therefore, without the benefit of Applicant's specification, one of skill could not have reliably predicted a method that looked at the level of regulatory T cell activity in the treatment of Th1 or Th2 related diseases after the administration of a helminthic parasite preparation. Without evidence that one of skill in the art could have predictably arrived at the claimed invention based on the teachings of WO 99/33479, and not based on the teachings of the instant specification, a *prima facie* case of obviousness under KSR has not been achieved.

### Conclusion

Applicant submits that all claims are allowable as written and respectfully requests early favorable action by the Examiner. If the Examiner believes that a telephone conversation with Applicant's attorney's/agent would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney/agent

of record.

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